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EP 0348696 A EP 0124200 A

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(54) Radiofrequency plasma biocompatibility treatment of medical devices

(57) Polymeric surfaces of medical devices are provided that have enhanced biocompatibility properties. The biocompatibility enhancing agent which contains acid groups is secured to the polymeric substrate by a spacer molecule containing amine groups which is covalently bound to the internal polymeric surface which had been subjected to radiofrequency plasma treatment with a plasma medium of water vapor, oxygen or combination of water vapor and oxygen gas. Internal polymeric surfaces are treated by using a very low pressure plasma medium.

The spacer amine is preferably albumin, urokinase, streptokinase or polyethyleneimine and the biocompatability enhancing agent is preferably heparin, hirudin, hyaluronic acid, streptokinase or urokinase.

The polymeric surface presents an anti-thrombogenic, fibrinolytic or thrombolytic interface with body fluids such as blood flowing through medical device tubing during implantation for medical procedures.

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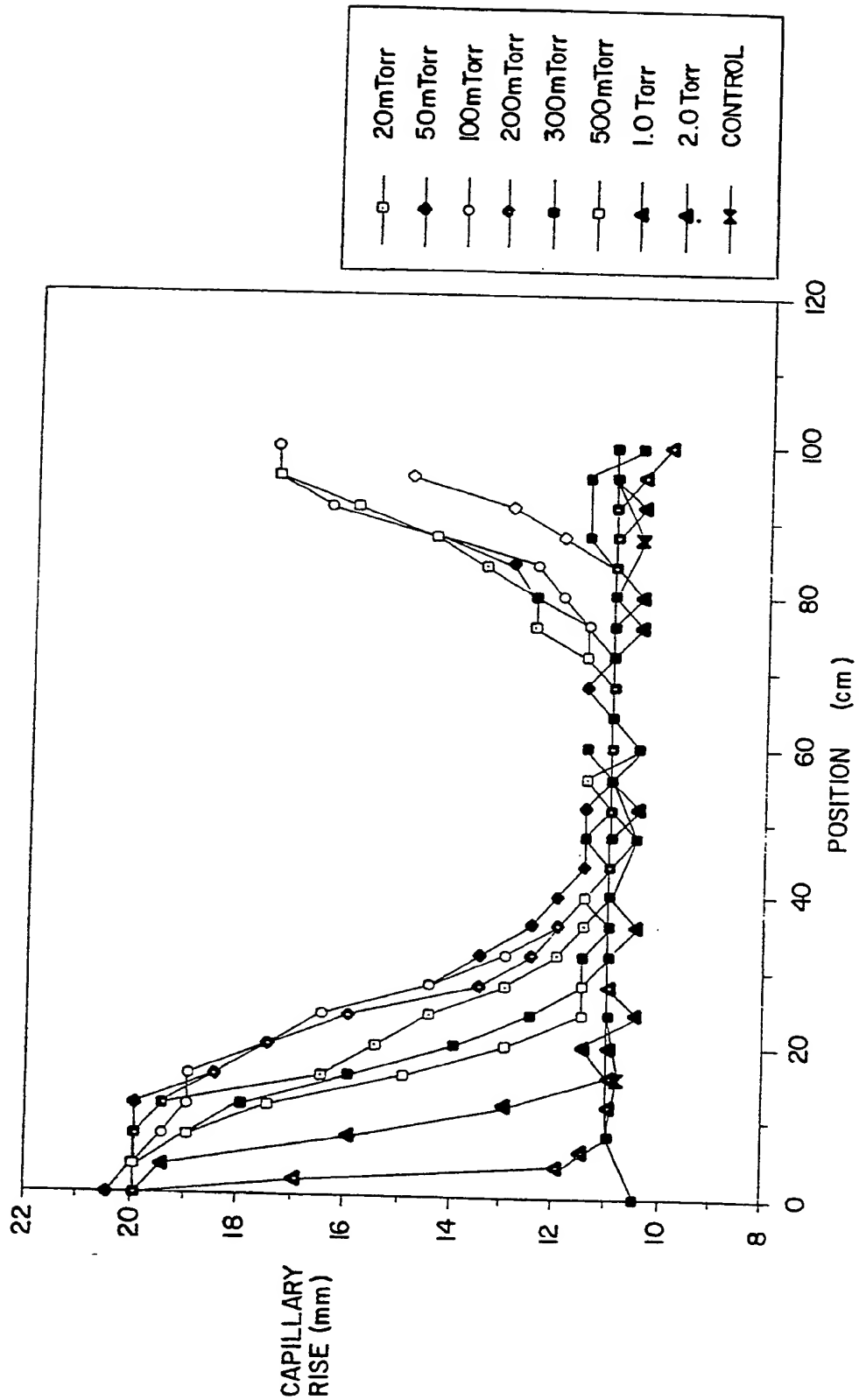
20mTorr
50mTorr
100mTorr
200mTorr
300mTorr
500mTorr
1.0 Torr
2.0 Torr
CONTROL
CAPILLARY RISE (mm)
POSITION (cm)
22
20
18
16
14
12
10
8
0
20
40
60
80
100
120

FIG-2

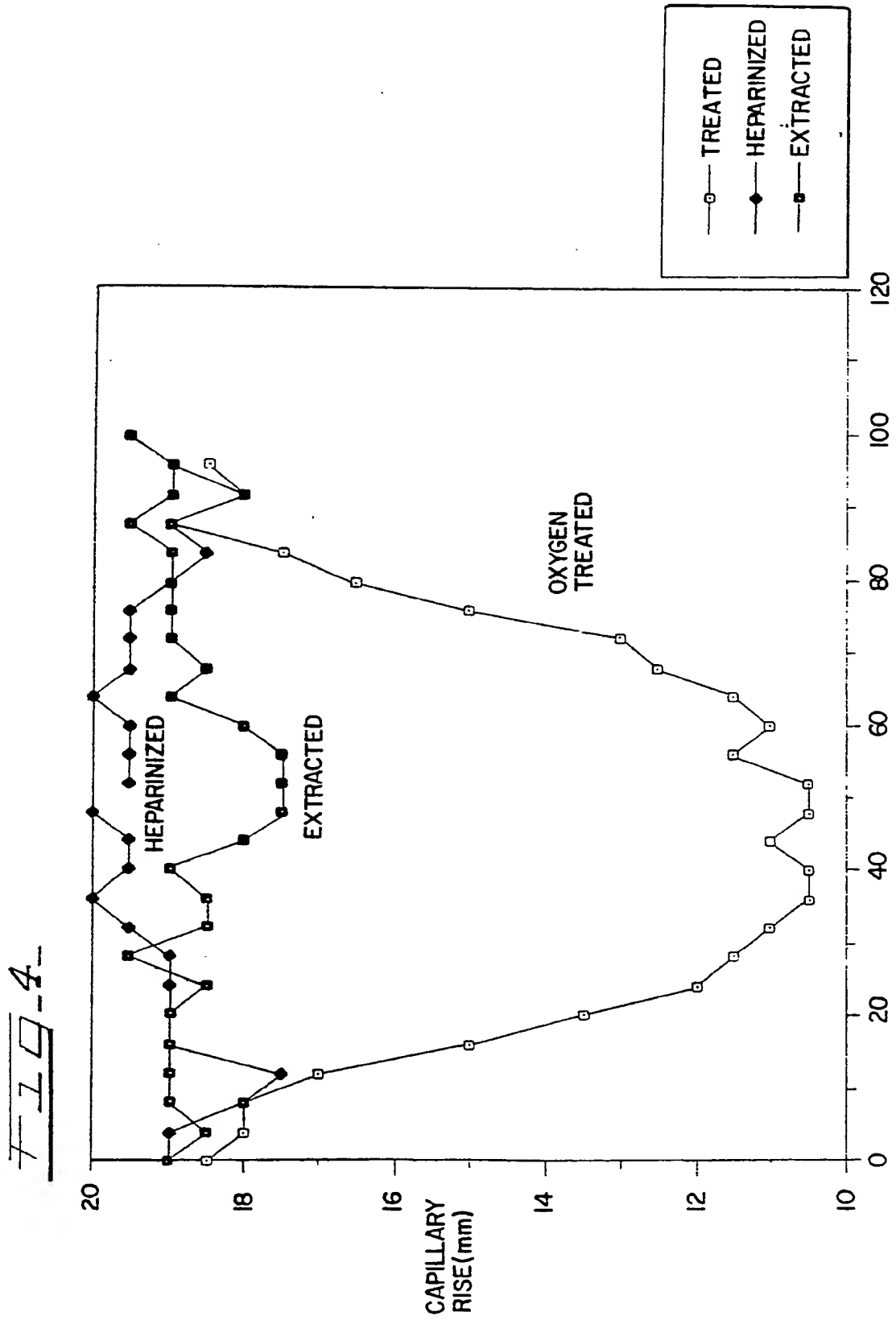

FIG-4

such as are encountered by medical devices that engage blood or other body fluids. At times, these surfaces in need of biocompatibility enhancement are partially enclosed interior surfaces such as lumens of catheters or other medical tubing.

Certain attempts have been made and approaches have been suggested whereby a polymeric surface is activated by treatment with a plasma which in turn reacts with heparin or the like to provide a polymeric surface having anti-thrombogenic properties. Included are patents incorporating plasma discharge treatment with a gaseous environment having a variety of gases, including inert gases and organic gases. Patents in this regard include U.S. Patents No. 4,613,517, No. 4,656,083 and No. 4,948,628, which mention a variety of plasma media including those generated from hydrogen, helium, ammonia, nitrogen, oxygen, neon, argon, krypton, xenon, ethylenic monomers and other hydrocarbons, halohydrocarbons, halocarbons and silanes. It will be appreciated that various ones of these plasma media are relatively expensive and can be hazardous to use within a manufacturing environment and/or to dispose of as waste. Also, certain plasma media are more suitable for treatment of specific substrates.

It is desirable to provide a surface treatment procedure which is available for use in connection with rendering anti-thrombogenic any of a number of surfaces of medical devices or the like, in some instances including partially enclosed interior surfaces. It is further desirable that any plasma deposition procedure included in this regard avoid the need to use plasma media that are expensive, potentially hazardous or otherwise difficult to handle. At the same time, any plasma media should strongly bind the anti-thrombogenic agent to the surface being treated, preferably while also accomplishing this in an especially efficient manner that is readily susceptible to use on a large scale.

device or out of the partially enclosed interior surface such as the tubing lumen.

It is accordingly a general object of the present invention to provide an improved method for treating polymeric surfaces and medical devices or the like having such surfaces with anti-thrombogenic agents or the like immobilized thereon, using radiofrequency plasma discharge techniques, and covalently binding anti-thrombogenic agents or the like to polymeric surfaces so that the agents do not leach away in wet in vivo conditions from the improved polymeric surfaces thus produced.

Preferably the present invention renders medical device polymeric surfaces anti-thrombogenic through a process that is relatively independent of the particular surface and the shape or geometry thereof.

Preferably the present invention provides a modified polymeric surface for a medical device component that exhibits biocompatibility over a polymeric surface not treated according to the method of the present invention.

One embodiment of the present invention avoids the need for specifically designed plasma treatment equipment when treating interior polymeric surfaces and provides an improved process for rendering interior surfaces of medical device components, such as narrow tubing, anti-thrombogenic through a process by which the mean free path of the gaseous treatment media generally approximates the dimensions of the interior volume such as the inside of medical grade tubing, whereby the reactive species are able to penetrate

must have overall properties which, except for thrombus concerns, render the polymers suitable for the surface of a medical device made in accordance with the present invention.

In accordance with the invention, these types of polymeric surfaces are made more suitable for long-term or short-term contact with flowing blood or other body fluids. This is accomplished by attaching an anti-thrombogenic agent, fibrinolytic agent or thrombolytic agent to the surface or device. These agents are used in relatively small amounts, and they are attached in such a manner that they remain biologically active, while at the same time being affixed to the polymeric surface in so secure a manner that the agents will not leach away in wet *in vitro* or *in vivo* environments.

Securement of the anti-thrombogenic agent or the like onto the polymeric surface includes positioning the tubing or the like having the polymeric surface within an apparatus to provide a radiofrequency plasma discharge environment. Devices for providing such an environment are generally known in the art. Typical devices in this regard are shown, for example, in U.S. Patents No. 4,632,842 and No. 4,656,083, the subject matter thereof being incorporated by reference hereinto. In devices used according to this invention, a reactor chamber is provided, and the device having the surface to be treated is simply inserted into the chamber without requiring any special structures or positioning. Especially when interior surfaces are to be treated, the chamber is evacuated by a suitable vacuum pump or the like, typically to a pressure below the treatment pressure targeted for the radiofrequency plasma discharge.

A source of fluid which provides the plasma environment then is fed into the chamber, and the desired treatment pressure for the plasma medium is developed and/or maintained. Glow discharge is induced within the reactor chamber by an electrode assembly disposed about

mixture can have as low as about 40% by volume of water vapor. When water vapor and oxygen are included in the plasma gas within the chamber, the preferred volume of water vapor is between about 40 and about 90 volume percent, with the balance being oxygen. It will be appreciated by those familiar with plasma discharge techniques that these volume percents are as present within the chamber at any instant in time because these are flowing fluids.

Concerning the treating fluid or plasma medium to be maintained during radiofrequency plasma surface modification of narrow internal surfaces, the pressure should not exceed about 0.033 kPa (0.25 Torr), typically less than about 0.027 kPa (0.2 Torr). Generally speaking, the water vapor and/or oxygen plasma gas pressure will be no lower than 1.3 Pa (0.01 Torr). Preferably, the treatment pressure should be maintained below about 0.013 kPa (0.1 Torr). At these reduced pressures, an average gaseous molecule will travel longer before it encounters another gaseous molecule. In gaseous kinetics, this is referred to as the mean free path. This longer mean free path at reduced pressures results in increased diffusion length of the reactive species, as well as of other species in the plasma species. If the dimension of a confined volume, such as the diameter of a tubing, is comparable to the mean free path of the reactive species, there is a much higher probability that the reactive species entering within the interior surface will collide with the wall of the device rather than undergo a gas phase collision. These wall collisions cause the inside surface to be chemically functionalized as required by the present invention.

These specific conditions can be used to deposit thin films on the inside surfaces using depositing monomers as plasma media. By the procedure according to the invention, the internal surfaces or lumens of tubings having an internal diameter of 1.8 mm (0.072 inch) or lower and a length of up to about 1.2 m (4 feet) is successfully treated.

containing approximately one percent by weight of PEI. Typically, the spacer component will be present at a concentration of between about 1.0 and about 5.0 weight percent, based upon the weight of the spacer solution.

A suitable anti-thrombogenic, fibrinolytic or thrombolytic agent is then covalently bound to the spacer group, also by means of condensation or trans-esterification chemistry. It is preferred that the agent exhibit acid functionality, whereby the carboxyl groups form a covalent linkage with amine groups of the spacer component. The resultant device has an anti-thrombogenic internal surface from which the anti-thrombogenic agent does not readily leach.

Exemplary anti-thrombogenic agents include heparinous components such as heparin, hirudin, heparin-albumin conjugates, hyaluronic acid, and the like. Illustrative fibrinolytic or thrombolytic agents include streptokinase, urokinase, and the like. Combinations of spacer component and of anti-thrombogenic agent or the anti-thrombogenic agent by itself can be used in the anti-thrombogenic agent composition which is attached to the modified polymeric surface having reactive sites. The anti-thrombogenic agent or the like is applied in the form of a solution having between about 10 and about 20 weight percent of anti-thrombogenic, fibrinolytic or thrombolytic agent, based upon the total weight of the composition.

The following examples illustrate the process and product, as well as performance results.

Example 1

Nylon 12 tubing having an inner diameter of 1.4 mm (0.055 inch) and a length of 100 cm (39 inches) was treated in a tubular radiofrequency plasma reactor. The plasma was created in the tubular chamber by capacitively coupling the RF at one end of the tubular reactor so that the visible part of the plasma was confined to one end of the tubing. Oxygen was the plasma medium. It was present at

of operating pressure for constant treatment time, plotting capillary rise versus position along the length of tubing prior to severance. The areas which received minimal treatment were at and near the midpoint along the length of the tubing. It will be appreciated from these data that, as the pressure of operation is reduced, the gradient becomes smaller indicating that the treatment length becomes longer. The central areas which received minimal treatment were more extensive or longer at the higher pressures than at the lower pressures, as can be seen in Figure 2. The control plot is of a totally untreated Nylon 12 tube which was subjected to the capillary test.

Example 3

Tests were conducted as described in Example 1, this time varying the operating pressure. The change of treatment length as a function of operating pressure data are reported in Figure 3. In this Figure, the length of the treated tubing at which the capillary rise is 3mm above the control value is plotted as a function of the operating pressure for different treatment times. The control sample had a capillary rise value of 10.3 $\pm$ 0.3mm. The power applied was constant, and three different treatment times were utilized, as reported in Figure 3.

Example 4

Tubing as described in Example 1 was subjected to radiofrequency plasma deposition from an oxygen medium. The treatment was carried out within a commercial reactor, a Model 7104 unit of Branson International Plasma Corporation. This commercial equipment included seven trays, and the tubing was laid upon the trays for treatment according to the invention. The control sample had a capillary rise value of 10.3 $\pm$ 0.3mm. The treatment pressure in the radiofrequency reactor was about 0.03kPa (230 milliTorr). The thus modified tubing was then treated with

Positive test results indicated the immobilization of heparin on both surfaces.

Example 6

High density polyethylene tubing having an internal diameter of 0.051 inch and a length of 30cm (12 inches) was treated in a water vapor plasma for 10 minutes at a pressure of 0.013kPa (0.1 Torr) and under 20 watts of radiofrequency power. The thus treated tubing was treated both on the outside and within the lumen with heparin. Both surfaces were then tested for the presence of heparin as described in Example 4, the tests positively indicating the presence of heparin.

Example 7

Tubing of the type described in Example 6 was treated in a radiofrequency plasma containing a medium of a mixture of water and oxygen at a pressure of 0.013kPa (0.1 Torr). The power supply was set at 20 watts. Heparinization followed, and the heparinized surfaces were tested, thereby indicating the presence of immobilized heparin within the lumen as well as on the outside surface of the tubing.

Example 8

Nylon 12 tubing having the size specified in Example 1 was treated in radiofrequency plasma using the same process conditions as in Example 1. In this Example 8, the two ends of the tubing were looped into 360 degree loops and into an ellipsoidal shape. The treated samples were tested in accordance with the capillary rise techniques discussed hereinabove. The results were comparable to those for straight elongated tubing, thereby indicating that the ends of the tubing need not be straight for the treatment to be effective within the lumen, provided the low pressure processing according to the present invention is achieved. In fact the treatment

seventy-two hours. Each sample and control was contacted with toluidine blue to determine the presence of heparin. Each of the samples stained purple, which indicates the presence of heparin on the surface of each of them. The intensity of the staining did not vary from the initial samples to those extracted for seventy-two hours. The controls, which were heparinized and extracted in PBS, exhibited no signs of color change upon staining.

Example 11

Samples of substrates treated in accordance with Example 9 were subjected to *in vitro* extraction conditions in 4M guanidine hydrochloride for one hour at room temperature. Other virtually identical samples were not subjected to extraction conditions. The extract was then assayed using a dimethylmethylene blue colorimetric assay which measures the purple shift in the presence of heparin. The extracted samples were also stained with toluidine blue to detect any heparin that might have been present. No heparin concentration was evident in the guanidine extract, which indicates that no heparin was removed by the guanidine. All of the extracted samples stained purple in toluidine blue with no variation in intensity from the non-extracted samples.

Example 12

Samples were made substantially in accordance with Example 9, except radiolabeled heparin was used. The heparin was labeled using ^{99m}Tc. The samples were counted using a gamma counter, and calculations were performed to determine the actual amount of heparin on the surface of the polymer. The counter detected an initial concentration of heparin of from 8 to 10 micrograms per square centimeter. After extraction with human blood plasma at 37°C. for three hours, the heparin concentration was detected at from 5 to 8 micrograms per square centimeter.

plasma reactor. The reactor was pumped down to below 1 mtorr, water vapor and oxygen were brought into the reactor until the pressure rose to the 200-400 mtorr range, and an RF power of 20 watts was applied to create a plasma. A number of runs were made, with the plasmas varying from 80% water vapor and 20% oxygen to 50% water vapor and 50% oxygen, as measured by a gas analyzer. The samples were treated for about 20 seconds and heparinized as in Example 9 and stained with toluidine blue.

A second type of sample was treated in the same way as the first ones, except that there was no oxygen brought into the reactor. This sample was heparinized and stained with toluidine blue. A third type of sample was treated with only oxygen plasma, and this sample was heparinized and stained with toluidine blue.

It was found that the sample which was oxygen plasma treated and subsequently heparinized gave a non-uniform staining compared to the water plasma-or water/oxygen plasma-treated samples. Each of the water plasma-and water/oxygen-plasma treated samples showed uniform staining, but the water/oxygen plasma-treated and subsequently heparinized sample showed a more intense staining than the sample treated in water plasma only and heparinized subsequently.

Example 16

A polyurethane-polyether copolymer (Pellethane) substrate was treated with a water/oxygen plasma at a 4:1 ratio following the procedure described in Example 8 and subsequently heparinized as in Example 9. The heparinized sample was tested for covalent binding of heparin with positive results.

Example 17

A nylon-polyether copolymer (Vestamid from Huls) was treated with a water/oxygen plasma as described in Example 15 and heparinized as in Example 9, except that

made by those skilled in the art without departing from the true spirit and scope of the invention.

3. A method for enhancing the biocompatibility of interior polymeric surfaces of medical device components, comprising the steps of:

positioning a medical device component having a polymeric surface within a radiofrequency plasma discharge apparatus;

providing a reduced pressure environment within the radiofrequency plasma discharge apparatus, said reduced pressure environment being on the order of 0.033 kPa (0.25 Torr) or less;

inserting into said reduced pressure environment a plasma medium selected from water vapor, oxygen gas, and the combination of water vapor and oxygen gas, said plasma medium having a pressure not greater than about 0.033 kPa (0.25 Torr);

subjecting said plasma medium to a radiofrequency electric field to induce a gas discharge in order to form reactive species within the plasma discharge apparatus and within the partially enclosed interior polymeric surface to form a modified partially enclosed interior polymeric surface which had been modified by the subjecting step;

treating said modified partially enclosed interior polymeric surface with a spacer component having amine groups whereby covalent linkages are formed between the spacer component amine groups and the reactive sites of the modified partially enclosed interior polymeric surface to form a spacer component-treated modified polymeric surface; and

contacting an anti-thrombogenic, fibrinolytic or thrombolytic agent having acid functionality and biologically active properties with the spacer component-treated modified polymeric surface, so that said partially enclosed modified polymeric surface is a biocompatible surface and the anti-thrombogenic, fibrinolytic or thrombolytic agent of the biocompatible surface is resistant to extraction

component-treated modified polymeric surface with a heparinous component.

11. The method in accordance with any of claims 1-10, wherein the plasma discharge environment is evacuated prior to the water vapor inserting step.

12. The method in accordance with any of claims 1-11, wherein the positioning step is preceded by pretreating a silicone rubber polymeric surface with an inert gas plasma deposition procedure.

13. The method in accordance with any of claims 3-12, wherein the positioning step places a tubing having a lumen as the partially enclosed interior polymeric surface having a diameter of less than about 2.5 mm (0.1 inch) and having a length suitable for use as a catheter for diagnostic or interventional uses.

14. A medical device component having a biocompatible polymeric surface, wherein the biocompatible polymeric surface comprises a surface which has been modified by subjecting the polymeric surface to radiofrequency discharge treatment within a plasma medium having at least about 40 volume percent water vapor, based upon the total volume of plasma medium, followed by treatment with a spacer component having amine groups forming covalent linkages with the polymeric surface which had been subjected to radiofrequency discharge treatment with said plasma medium, after which an anti-thrombogenic, fibrinolytic or thrombolytic agent having acid functionality had contacted and covalently bonded with the spacer component-treated polymeric surface to provide the biocompatible polymeric surface.

is a component of a diagnostic catheter, an interventional catheter, a cannula or a medical device balloon catheter.

19. The medical device component in accordance with any of claims 14-18, wherein said covalent linkages between the modified polymeric surface and the spacer component are between carboxyl or hydroxyl groups formed by the radiofrequency discharge treatment on the polymeric surface and primary or secondary amine groups of the spacer component.

20. The medical device component in accordance with claim 19, wherein a covalent linkage is present between primary or second amine groups of spacer component molecules and the acid functionality groups of the anti-thrombogenic, fibrinolytic or thrombolytic agent.

21. The medical device component in accordance with any of claims 14-20, wherein said polymeric surface is a silicone rubber component that been pretreated with an inert gas plasma.

22. The medical device component in accordance with any of claims 14-21, wherein said polymeric surface had been modified with a radiofrequency discharge treatment from said plasma medium which includes at least about 10 volume percent oxygen, based upon the total volume of the plasma medium.

23. The medical device component in accordance with any of claims 14-22, wherein said polymeric surface had been modified with a radiofrequency discharge treatment from said plasma medium which includes between about 40 and about 100 volume percent water

Patents Act 1977
Examiner's report to the Comptroll r under Section 17 (Th Search Report)

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Relevant T chnical fields

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(ii) Int Cl (Edition 5) A61L 33/00
C08J 7/12

Search Examiner

MISS D DAVIES

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASE: WPI

Date of Search

11 AUGUST 1992

Documents considered relevant following a search in respect of claims 1-25

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X	EP 0348969 A (BECTON DICKINSON COMPANY) use of oxygen in plasma activation	3
X	EP 0124200 A (BECTON DICKINSON COMPANY) use of oxygen in plasma activation	3

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